IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Manne Satyanarayana Reddy et al. Art Unit: 1625

ApplicaTion No.: 10/816,798 Examiner: C. C. Chang

Filed: April 2, 2004

For: NOVEL CRYSTALLINE FORM-VI OF DONEPEZIL HYDROCHLORIDE AND PROCESS FOR THE PREPARATION THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

REPLY BRIEF

This is submitted in response to the Examiner's Answer that was mailed on June 6, 2008. A supplemental Examiner's Answer was dated July 1, 2008 to add a heading to Section 11 ["Related Proceeding(s) Appendix"] of the original document, but the substantive content apparently was not changed and the original effective mailing date appears to apply.

Appellants have identified several significant errors in the arguments presented in the Examiner's Answer, and these will be addressed below.

A. Rejection Under 35 U.S.C. § 102(b).

In the Examiner's Answer, the Examiner erroneously argued that the appealed claims of the instant application are anticipated.

Appellants' claim 2 is illustrative for discussion purposes. Claim 2 clearly encompasses a single polymorphic form of donepezil hydrochloride known as Form VI and having a unique crystalline structure, which can be identified by reviewing its

powder X-ray diffraction ("PXRD") pattern. That pattern is provided in the specification, as filed, in Fig. 1.

The Examiner's Answer referred to a "comparative" representation of the patterns of Fig. 1 of the application and Fig. 3 from U. S. Patent 5,985,864 of Imai et al. ("the '864 patent"), in support of the rejection. However, the 2-theta scales for the two patterns are not the same and making a meaningful comparison is rather difficult. For this reason, Appellants have now reduced the scale of their Fig. 1 to closely correspond with that of the reference pattern, and are providing the appended copy (as Exhibit A) of a page that has the two patterns aligned by their degrees 2-theta, over the range of 5-30 degrees.

From the totality of a pattern, one having ordinary skill in the art should easily be able to ascertain whether or not an unknown form of that same drug was or was not the same crystalline form claimed. And, indeed, even to one knowing nothing about PXRD, comparing Fig. 3 from the '864 patent, which provides the PXRD pattern for a distinct crystalline form of that active known as Form III, with the PXRD pattern for Form VI of the claimed invention, leaves no doubt as to their distinctness.

As noted in Appellants' Appeal Brief, Form III has a peak at 6.5 degrees 2-theta but there is no peak in that location for Form VI. Also, Form VI has a peak at approximately 11.5 degrees 2-theta, while there is clearly no similar peak found in Fig. 3 of the '864 patent. These are but two of the manifest dissimilarities between the patterns of the two crystalline forms. There clearly are others. There are five peaks located between 10 and 15 degrees 2-theta in the PXRD pattern of Form VI, with the single largest peak in the pattern disposed between 12 and 13 degrees 2-theta (according to the application as filed, that peak can be found at about 12.7 degrees 2-theta (*see* Table 2 at page 6 of the specification). In contrast, there are at most three peaks (counting the shoulder to the right of the peak at about 13 degrees) in the pattern of Form III found in that same region. And no peak found in that portion of the PXRD pattern of Form III could be characterized as having the largest relative peak intensity. Indeed, no peak in that region is even in the top ten. However, in a more general sense, the human eye, even the untrained eye, would look at the overall patterns of these two materials and clearly discern that they are not identical. Claim 2 therefore

particularly points out and distinctly claims an invention different from that depicted in Fig. 3 of the '864 patent.

In an effort to address this critical flaw in the rejection, the Examiner pointed out that the claim includes the term "substantially" and that the pattern need not be exactly as shown but only "substantially as depicted in Fig. 1" (Examiner's Answer at page 4). However, use of the term "substantially" is a recognition that different equipment and techniques may be used in generating different patterns and may provide slight variations in relative peak heights or peak positions. Anyone of ordinary skill in the art of PXRD would understand that to be the case. In fact, as the Bernstein reference, cited by the Examiner, notes, the preparation of samples of powder diffraction can lead to differences (*id.* at page 5). Rather than supporting the Examiner's position, this supports Appellants' use of the word "substantially." Despite these possible variations, the art still recognizes PXRD as a diagnostic technique - one which allows trained observers to identify unique crystalline forms. This is because the types of "variations and inconsistencies" described by Bernstein can not explain the types of differences manifest from an overall comparison of the pattern of Form III as depicted in Fig. 3 of the '864 patent, and the pattern of Form VI as currently claimed.

Accompanying this document is a portion of a chapter entitled "Methods for the Characterization of Polymorphs and Solvates," from the book by H. G. Brittain, ed., *Polymorphism in Pharmaceutical Solids*, Marcel Dekker, Inc., New York, 1999, pages 227-238. In the paragraph bridging pages 228 and 229, the author states:

> However, it cannot be overemphasized that the defining criterion for the existence of polymorphic types must always be a nonequivalence of crystal structures. For compounds of pharmaceutical interest, this ordinarily implies that a nonequivalent x-ray powder diffraction pattern is observed for each suspected polymorphic variation. All other methodologies must be considered as sources of supporting and ancillary information; they cannot be taken as definitive proof for the existence of polymorphism by themselves alone.

Also instructive is the first paragraph on page 236, where the author states:

> Since every compound produces its own characteristic powder pattern owing to the unique crystallography of its

> structure, powder x-ray diffraction is clearly the most powerful and fundamental tool for a specification of the polymorphic identity of an analyte.

Taken to its logical endpoint, the Examiner's position would allow one to liken any PXRD pattern to any other, as they all have a number of peaks and some of those peaks may be in the same vicinity. Couldn't any pattern be "substantially" that of any other? Clearly, the answer is "no." And, just as clearly, the PXRD pattern of the presently claimed Form VI is not substantially that of Form III.

Nor should one lose sight of the purpose of claim 2 - to claim a unique crystalline form of the molecule. Therefore, the question is whether the patterns are equivalent, that is, whether or not they allow one of ordinary skill in the art to discern that the claimed crystalline form is different from any crystalline form(s) disclosed in the art.

The importance of this point, that the claim is not to a pattern, but to a unique crystalline form, is amplified by consideration of the Examiner's observations on melting point. Melting point is an analytical technique which can provide information useful in distinguishing molecules, including polymorphs. The melting point of Form VI is 222-225°C (application, at page 8), significantly lower than that of Form III which is reported in the '864 patent as being 229-231°C ('864 patent, at column 7, lines 13-14). The Examiner attempted to deal with this inconvenient truth by denigrating Appellants' data. The Examiner first suggested that Appellants' data is "confusing" and then suggested that the melting point data recited on page 8 of the application are "associated with decomposition" (Examiner's Answer at page 6). The Examiner went on to opine that "[i]t is common understanding by chemists that broad melting points with decomposition ordinarily relates to impurity of the product." (*Id.*)

Putting aside the complete lack of support on the record for the Examiner's description of "chemists' understandings," the very art upon which the Examiner relied distinguishes different polymorphic forms of this same molecule by reliance on their melting points (decomposition). And, the differences between melting point (decomposition) ranges for polymorphic forms described in the '864 patent are often less than the degree difference between the melting points of Forms VI and III (*see* the '864 patent, at column 7, lines 9-19). For example, the melting point range reported for

Form IV according to the '864 patent is 226-228°C, rather close to the 229-231°C range reported in the same table for Form III.

The art of record clearly advocates melting points (decomposition points) as being indicative of different polymorphic forms of donepezil hydrochloride, and there is a clear difference in the melting points of Forms VI and III. This coupled with the inescapable differences in the PXRD patterns of these two forms leaves no doubt that they are distinct and that Form VI is novel. Further, these same arguments apply to claims 3-6 and 8. While claims 3-5 recite different figures reflecting different analytical techniques, they all claim the same molecule as claim 2 and are distinct for the very same reason - that the polymorphic form is different from any of those found in the art.

The Examiner also attempted to deflect Appellants' arguments by pointing out that the melting point is not part of the claim. However, it needs not be. It has been recognized for many years that "a compound and all of its properties are inseparable; they are one and the same thing." *Application of Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). By claiming a particular molecule, in this instance by virtue of its PXRD pattern in claim 2 and Fig. 1, Appellants claim a unique crystalline form of donepezil hydrochloride. Appellants are not required to include within the same claim for that molecule a recitation of its other characteristics or properties.

B. Rejection Under 35 U.S.C. § 103(a).

Nor has the Examiner sustained the Office's burden of establishing a *prima facie* case of obviousness. Again claim 2 is illustrative. The Examiner looked at the various polymorphic forms, considered only the similarities in their analytical properties, and surmised that these polymorphs are therefore obvious. The plethora of polymorph patents issued by the U.S. Patent and Trademark Office stands testament to the fallacy of that logic. And, as was the case in the anticipation rejection, this position again evidences a misunderstanding of the data presented and its appropriate use.

Returning to melting point, for example, how can differences in melting point ranges equate directly to similarity in crystalline forms? The point is not that the melting point ranges are similar or close; and as noted above, in this case they are not very close. The point is that they are not the same, and necessarily the compounds that

each represent are different as well. Can't compounds with very different structures have similar melting point ranges? So how, just based on a similarity of melting points, can one conclude anything about the two molecules other than that they are different?

Nor can one looking at two possibly related PXRD patterns - and the patterns here are not identical, as discussed previously - tell anything other than that the respective forms are different? Appellants know of no direct correlation between "related" PXRD patterns and similarity of the molecules that generated those patterns. Identical patterns certainly identify molecules as the same. But related patterns provide no basis for one to speculate about the degree of similarity or dissimilarity between two distinct polymorphs.

One needs look no further than the '864 patent itself, which separately claims polymorphic Forms II, III, IV and V. As discussed previously, they all have "similar" melting point ranges. And a review of Figures 1-4 show PXRD patterns for four different forms that might be considered as "substantially" similar to each other, using the logic of the Examiner's Answer. Yet they were separately patentable. With all due respect, the Examiner's arguments miss the mark. These same comments are applicable to all of the claims.

The facts recited by Appellants in their Appeal Brief stand unrebutted. Even if "more than half of all pharmaceutical compounds exhibit polymorphism," a statement relied upon by the examiner (Doelker summary, discussed in the Examiner's Answer at 5), which is surely conjecture, many do not. And, there is presently no way of predicting which compounds are polymorphic and which are not. There are: 1) no way of knowing if a compound will have polymorphs; 2) no way of knowing how many polymorphs there will be, if indeed any; and 3) no way of knowing which polymorph will be produced by which process.

The Examiner's dubious reliance on an entry in Wikipedia.com is perhaps most illustrative of the fallacies of the Examiner's position. The examiner argued that "... every compound has different polymorphic forms and that in general the number of forms known for a given compound is proportional to the time and money spent in research on that compound' (Wikipedia)" (Examiner's Answer, at page 5). Three points should be made. First, one pundit's unsupported statement that more than half of all

pharmaceutical compounds have polymorphs, must be reconciled with the very next pundit cited, saying all compounds have polymorphs. Which is it? Most likely, neither. Second, many important scientific discoveries are proportionate to the amounts of time and money expended. That statement, even if correct, which it is not, is hardly a justification for denying anyone a patent. Third, unsubstantiated quotes from real and cyber pundits cannot mask the infirmities of the Examiner's position. Despite the probable considerable expenditures of time and money by Imai et al., the '864 patent is not a complete catalog of all of the polymorphic forms of this particular molecule. Form VI was not known to those who invented the '864 patent nor was their expenditure of time and money apparently sufficient to place them in the possession of Form VI. The general knowledge that polymorphs existed did not drive them to find Form VI. On this record, there is nothing that explains why one would even look for more polymorphs, why one would have a reasonable expectation of finding additional polymorphs, and most importantly, why they would have a reasonable expectation of finding Form VI. Form VI is unobvious, under the applicable law.

C. Objection Under 35 U.S.C. § 1.75(c).

Claims 8-12 have also been objected to pursuant to 35 C.F.R. § 1.75(c) for allegedly being of improper dependent form. More particularly, they allegedly fail to further limit the subject matter of the base claim. Appellants again respectfully traverse this objection, noting that the Examiner cited nothing to support the Examiner's position. It is clear that claim 2 is specific to a molecule having a particular PXRD pattern. That claim, as a product claim, is not bound by any particular process. No matter how one manufactures that particular material, they would fall within the scope of claim 2. That is not the case for claim 8. Claim 8, for example, clearly requires that a material falling within the scope of claim 2 be produced by combining a solution of donepezil hydrochloride and an alcohol with an ether followed by separating Form VI. As claim 8 clearly contains every limitation of claim 2, plus other limitations as well, it clearly does narrow the scope of claim 2. The same is true of claims 9-12.

Attention is drawn to the decision of *In re Hughes*, 496 F.2d 1216 (CCPA 1974), wherein it is stated at 1219:

> Furthermore, even if it is shown that the product can be broadly defined solely in terms of structure and characteristics, appellant makes the point, with which we agree, that where his product is incapable of description by product claims which are of a *different* scope, he is entitled to product-by-process claims that recite his novel process of manufacture as a hedge against the possibility that his broader product claims might be invalidated. (emphasis in original)

Appellants' inclusion of both product and product-by-process claims is not inherently wrong or duplicative, and the objection is not proper.

CONCLUSION

In view of the unsupported and unsupportable conclusions in the Examiner's Answer, the rejections of Appellants' claims was improper and should not be sustained. Reversal is therefore respectfully solicited.

Respectfully submitted,

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August 5, 2008

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EXHIBIT A

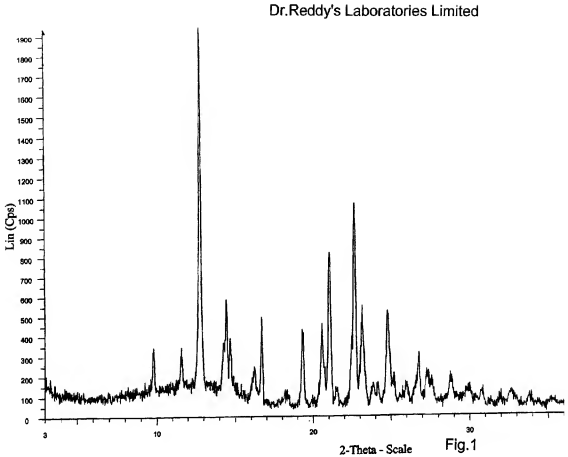
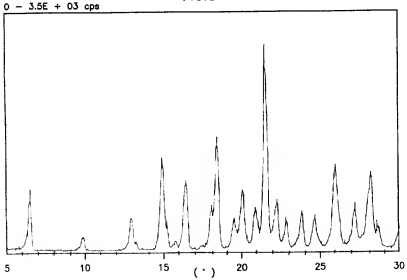


Fig.1

FIG.3



Polymorphism in Pharmaceutical Solids

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6

Methods for the Characterization of Polymorphs and Solvates

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I. INTRODUCTION

Certainly the most important aspect relating to an understanding of polymorphic solid and solvate species is the range of analytical methodology used to perform the characterization studies [1–3]. The importance of this area has been recognized from both scientific and regulatory concerns, so the physical methods have begun to come under the same degree of scrutiny as have the traditional chemical methods of analysis. Byrn et al. have provided a series of useful definitions that concisely give the characteristics of the various solid forms that can be found for a given drug substance [4] and that will be used throughout this chapter. Compounds may be *polymorphs* (forms having the same chemical composition but different crystal structures), *solvates* (forms containing solvent molecules within the crystal structure), *desolvated solvates* (forms when the solvent is removed from a specific solvate while still retaining the original crystal structure), or *amorphous* (solid forms that have no long-range molecular order).

Of all the methods available for the physical characterization of solid materials, it is generally agreed that crystallography, microscopy, thermal analysis, solubility studies, vibrational spectroscopy, and nuclear magnetic resonance are the most useful for characterization of polymorphs and solvates. However, it cannot be overemphasized that the defining criterion for the existence of polymorphic types must always be a nonequivalence of crystal structures. For compounds of pharmaceutical interest, this ordinarily implies that a nonequivalent x-ray

powder diffraction pattern is observed for each suspected polymorphic variation. All other methodologies must be considered as sources of supporting and ancillary information; they cannot be taken as definitive proof for the existence of polymorphism by themselves alone.

In the present work, the practice of the most commonly encountered techniques performed for the solid-state characterization of polymorphic or solvate properties will be reviewed. No attempt will be made to summarize every recorded use of these methodologies for such work, but selected examples will be used to illustrate the scope of information that can be extracted from the implementation of each technique.

II. CRYSTALLOGRAPHY: X-RAY DIFFRACTION

The x-ray crystallography technique, whether performed using single crystals or powdered solids, is concerned mainly with structural analysis and is therefore eminently suited for the characterization of polymorphs and solvates. An external examination of crystals reveals that they often contain facets, and that well-formed crystals are completely bounded by flat surfaces. Planarity of this type is not commonly encountered in nature, and it was quickly deduced that the morphological characteristics of a crystal are inherent in its interior structure. In fact, the microscopic form of a crystal depends critically on structural arrangements at the atomic or molecular level; the underlying factor controlling crystal formation is the way in which atoms and molecules can pack together.

A. Single Crystal X-Ray Diffraction

Every crystal consists of exceedingly small fundamental structural units that are repeated indefinitely in all directions. In 1830, Hessel conducted a purely mathematical investigation of the possible types of symmetry for a solid figure bounded by planar faces and deduced that only 32 symmetry groups were possible for such objects. The same conclusion was reached by Bravais in 1949 and Gadolin in 1867. These 32 crystallographic point groups are grouped into six crystal systems,

denoted triclinic, monoclinic, orthorhombic, tetragonal, trigonal, hexagonal, and cubic. Each crystal system is characterized by unique relationships existing among the crystal axes and the angles between these, and this information is summarized in Table 1.

One of the characteristics of many crystals is their ability to be split along certain directions, yielding fragments containing smooth faces along the direction of the break. The angular relations between these cleavage planes were found to be the same in every fragment. Ultimately, it was learned that crystal cleavage planes corresponded to planes of atoms or molecules in the crystal, which in turn resulted from the repetition of unit cells. This three-dimensional pattern of atoms in a crystalline solid was shown to be capable of acting as a diffraction grating to light having wavelengths of the same order of magnitude as the translational repeat period of the molecular pattern. This period is

Table 1 Characteristics of the Six Crystal Systems

System	Description
Cubic	Three axes of identical length (identified as a_1, a_2, and a_3) intersect at right angles.
Hexagonal	Four axes (three of which are identical in length, denoted a_1, a_2, and a_3) lie in a horizontal plane and are inclined to one another at 120°. The fourth axis, c, is different in length from the others and is perpendicular to the plane formed by the other three.
Tetragonal	Three axes (two of which are denoted a_1 and a_2 and are identical in length) intersect at right angles. The third axis, c, is different in length with respect to a_1 and a_2.
Orthorhombic	Three axes of different lengths (denoted a, b, and c) intersect at right angles. The choice of the vertical c axis is arbitrary.
Monoclinic	Three axes (denoted a, b, and c) of unequal length intersect so that a and c lie at an oblique angle and the b axis is perpendicular to the plane formed by the other two.
Triclinic	Three axes (denoted a, b, and c) of unequal length intersect at three oblique angles.

of the order of 10^{-10} meters (i.e., angstrom units), and light having wavelengths of this magnitude is called x-ray radiation. The discovery that x-rays could be diffracted by crystalline solids was made by von Laue and his collaborators, and the method was quickly improved by Bragg and subsequently developed by countless others. It must be emphasized, however, that it is the electron density about an atom that is responsible for the scattering of x-rays by matter.

All x-ray diffraction techniques are ultimately based on Bragg's law, which describes the diffraction of a monochromatic x-ray beam impinging on a plane of atoms [5]. Parallel incident rays strike the crystal planes at an angle θ and are then diffracted at the same angle. The observation of reinforcement requires that the path difference of the impinging beam (i.e., the distance between molecular planes) be equal to a whole number of wavelengths. The scattering angles are therefore correlatable to the spacings between planes of molecules in the lattice by means of Bragg's law:

$$n\lambda = 2\,d \sin \theta \tag{1}$$

where

n = order of the diffraction pattern
λ = wavelength of the incident beam
d = distance between the planes in the crystal
θ = angle of beam diffraction

It should be noted that the Bragg equation yields only the scattering angles with respect to the incident x-ray beam and has nothing to say about the relative intensities of diffracted radiation. To describe scattered intensities, one uses the concept of the scattering power of a sample. This is equal to the number of free and independent electrons, scattering according to Thompson's law governing the scattering by a free electron, which would be required to replace the object in order to obtain the same scattered intensity.

A determination of the internal structure of a crystal requires the specification of the unit cell dimensions (axis lengths, and angles between these) and measurement of the intensities of the diffraction pattern of the crystal. For a given lattice, regardless of the content of the

unit cell, the directions of reflection are the same. The experimental determination of these directions is used to deduce the reciprocal lattice of the crystal, which unambiguously yields the crystal lattice. In addition, the relative intensities diffracted by different planes depend on the contents of the unit cell. Their measurement leads to the determination of the crystal structure factor, and these data permit the determination of the atomic structure of crystals. More detailed expositions of the procedures used to obtain the structures of single crystals are available in the literature [5–9] and are beyond the scope of this article.

Genuine polymorphism ordinarily arises either from differences in the packing of conformationally equivalent molecules or from different modes of assembly of conformationally inequivalent molecules. The former situation is well-known for inorganic and geological crystals [10], and the latter has been discussed in detail [11]. One of the best known instances of packing polymorphism are the allotropes of carbon, graphite and diamond. As shown in Fig. 1, in diamond each carbon atom is tetrahedrally surrounded by four equidistant neighbors, and the tetrahedra are arranged to give a cubic unit cell. Graphite is composed of planar hexagonal nets of carbon atoms, which can be arranged to yield either a hexagonal unit cell (the α-form) or a rhombohedral unit cell (the β-form).

Two anhydrous polymorphs of nitrofurantoin have been reported [12], as well as two polymorphic monohydrate forms [13]. In the triclinic α-anhydrate form, the nitrofurantoin molecules were found to be associated in a head-to-head manner, forming centrosymmetric dimer units through two identical intermolecular hydrogen bonds, with these dimer units being further linked into sheets by a system of weaker hydrogen bonds. The hydrogen bonding existing in the molecular planes of the monoclinic β-anhydrate form was found to differ in symmetry, where the key hydrogen bond was seen to link nitrofurantoin molecules by a twofold screw-axis [12]. In each of the two monohydrate forms, the conformations of the nitrofurantoin molecules are essentially equivalent to each other and not significantly different from the conformation observed for the anhydrate forms. However, the hydrogen bonding pattern induced by the presence of lattice water molecules yields two very different packing modes for the two monohydrate polymorphs. In the monoclinic form, virtually all of the atoms lie in

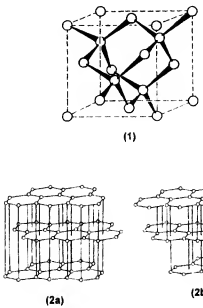

Fig. 1 Crystal structure of (1) diamond, showing the tetrahedral coordination of each carbon atom. Also shown are the crystal structures of the two polymorphs of graphite, specifically (2a) the hexagonal α-form and (2b) the rhombohedral β-form.

a single plane, giving rise to a completely layered structure. In the orthorhombic form, layers of molecules are arranged parallel to different planes, so the overall packing is that of a herringbone arrangement [13].

Probucol is an example of a compound where the polymorphism arises from the packing of different conformers [14]. Although both forms were found to be monoclinic, the unit cells belonged to different space groups and the molecular conformations of the title compound were quite different (Fig. 2). In Form II, the C–S–C–S–C chain is extended, and the molecular symmetry approximates C_{2v}. This symmetry is lost in Form I, where the torsion angles about the two C–S bonds deviate significantly from 180°. The extended conformer was shown to be less stable relative to the bent conformer, as simple grinding was sufficient to convert Form II into Form I.

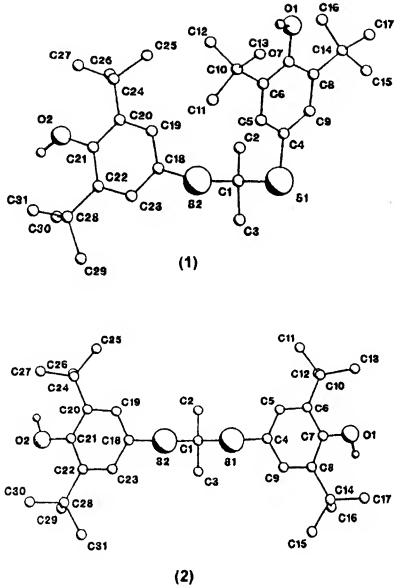

Fig. 2 Conformation of the probucol molecule existing in (1) Form I and (2) Form II. (The figure was adapted from data contained in Ref. 14).

Not all instances of conformational polymorphism are as dramatic as that just described, and often different conformers of a single side chain are able to pack into different crystalline arrangements. For instance, the two polymorphs of *p*-(1*R*,3*S*)-3-thioanisoyl-1,2,2-trimethylcyclopentane carboxylic acid were found to be associated with different conformations of the carboxylate group [15]. Torsion about a single C–N bond was shown to be the origin of the polymorphism detected for lomeridine dihydrochloride [16]. Finally, relatively small differences in molecular conformation were detected for the two polymorphic and four solvated crystalline forms of spironlactone [17].

B. X-Ray Powder Diffraction

Although the solving of a crystal structure provides the greatest understanding of polymorphic solids, the necessity for obtaining suitable single crystals and the degree of complexity associated with the data analysis preclude this technique from being used on a routine basis for batch characterization. In fact, most drug substances are obtained as microcrystalline powders, from which it is often fiendishly difficult to obtain crystallographically adequate crystals. Furthermore, during the most common evaluation of drug substances, it is usually sufficient to establish only the polymorphic identity of the solid and to verify that the isolated compound is indeed of the desired structure. For these reasons, and to its inherent simplicity of performance, the technique of x-ray powder diffraction (XRPD) is the predominant tool for the study of polycrystalline materials [18] and is eminently suited for the routine characterization of polymorphs and solvates.

A correctly prepared sample of a powdered solid will present an entirely random selection of all possible crystal faces at the powder interface, and the diffraction off this surface provides information on all possible atomic spacings in the crystal lattice. To measure a powder pattern, a randomly oriented sample is prepared so as to expose all the planes of a sample and is irradiated with monochromatic x-ray radiation. The scattering angle θ is determined by slowly rotating the sample and using a scintillation counter to measure the angle of diffracted x-rays with respect to the angle of the incident beam. Alternatively, the angle between sample and source can be kept fixed, and the detector

moved along a proscribed path to determine the angles of the scattered radiation. Knowing the wavelength of the incident beam, the spacing between the planes (identified as the d-spacings) is calculated using Bragg's law.

The XRPD pattern will therefore consist of a series of peaks detected at characteristic scattering angles. These angles, and their relative intensities, can be correlated with the computed d-spacings to provide a full crystallographic characterization of the powdered sample. After indexing all the scattered lines, it is possible to derive unit cell dimensions from the powder pattern of the substance under analysis [18]. For routine work, however, this latter analysis is not normally performed, and one typically compares the powder pattern of the analyte to that of reference materials to establish the polymorphic identity. Since every compound produces its own characteristic powder pattern owing to the unique crystallography of its structure, powder x-ray diffraction is clearly the most powerful and fundamental tool for a specification of the polymorphic identity of an analyte. The USP general chapter on x-ray diffraction states that identity is established if the scattering angles of the ten strongest reflections obtained for an analyte agree to within ± 0.20 degrees with that of the reference material, and if the relative intensities of these reflections do not vary by more than 20 percent [19].

The power of XRPD as a means to establish the polymorphic identity of an analyte can be illustrated by considering the case of the anhydrate and trihydrate phases of ampicillin. The crystal structures of both phases have been obtained, and they differ in the nature of the molecular packing [20]. The amino group in the monoclinic anhydrate is hydrogen bonded to the ionized carboxyl groups of two molecules, while the amino group of the orthorhombic trihydrate is hydrogen bonded to a single carboxylate group and to the waters of hydration that link other molecules in the structure. The powder patterns of these two materials are shown in Fig. 3 and are seen to be readily distinguishable from each other. Amoxycillin trihydrate has been found to crystallize in the same space group as does ampicillin trihydrate, and it exhibits a very similar pattern of hydrogen bonding [21]. However, the dimensions of the two unit cells differ significantly, and this fact is

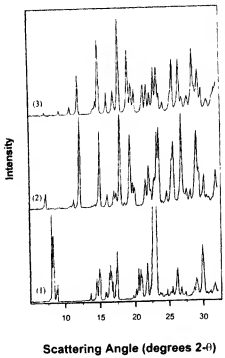

Fig. 3 X-ray powder diffraction patterns of (1) ampicillin anhydrate, (2) ampicillin trihydrate, and (3) amoxicillin trihydrate.

reflected in the differences among the relative intensities of the corresponding peaks contained in Fig. 3. Even though the two structures would be considered as being isostructural, the XRPD patterns of the two trihydrate phases readily permit an unambiguous identification and distinction between these.

X-ray powder diffraction can also be used for the quantitative determination of phase composition, and this approach has been discussed in detail [22]. In one particularly well-developed example, XRPD was used to quantitate the relative amounts of the anhydrate and dihydrate phases existing in carbamazepine samples [23]. The method was based on the observation that the XRPD of each phase

featured a scattering peak unique to each form, which was noted at a scattering angle where no scattering was observed for the other phase. Unlike loose powders, compressed samples yielded highly reproducible intensity values, so pelletized materials were used for the data acquisition. Good correlation between sample composition and scattering intensities was obtained in standard materials, permitting the generation of analytical relations suitable for the analysis of analyte samples.

The degree of crystallinity associated with a sample can often be established using powder x-ray diffraction. If the patterns of 100% crystalline and 100% amorphous material can be established, then the integrated peak intensity of the analyte is used to deduce the percent crystallinity. Such methodology has been used to measure the crystallinity of digoxin [24] and calcium gluceptate [25]. The XRPD method is extremely important during the characterization of lyophilized materials, since the stability of a crystalline solid is expected to exceed that of an amorphous or disordered solid. For instance, the technique has been used to study the properties of lyophilized imipenem [26].

III. MORPHOLOGY: MICROSCOPY

An extremely important tool for the characterization of polymorphs and solvates is that of microscopy, since the observable habits of differing crystal structures must necessarily be different and therefore useful for the characterization of such systems [27]. Common sense would dictate that the visual observation of such materials would immediately follow an x-ray crystallographic study, which would in principle make the science of optical crystallography [28–30] an essential aspect of any program of study. A review of crystallography from the pharmaceutical viewpoint is available [31].

As stated in an earlier section, a crystal is a polyhedral solid, bounded by a number of planar faces that are normally identified using the Miller indices. The arrangement of these faces is termed the *habit* of the crystal, and the crystal is built up through the repetition of the unit cell. The three-dimensional basic pattern of molecules in a solid